
2013 Cardiovascular Risk Standing Review Panel

*Research Plan Review for:
The Risk of Orthostatic Intolerance during Re-Exposure to Gravity*

*Status Review for:
The Risk of Cardiac Rhythm Problems*

Final Report

I. Executive Summary and Overall Evaluation

The 2013 Cardiovascular Risk Standing Review Panel (from here on referred to as the SRP) participated in a WebEx/teleconference with members of the Human Health Countermeasures (HHC) Element, representatives from the Human Research Program (HRP), and NASA Headquarters on January 10, 2014 (list of participants is in Section IX of this report). The SRP reviewed the updated Research Plan for the Risk of Orthostatic Intolerance (OI) during Re-Exposure to Gravity (OI Risk) and received a status update on the Risk of Cardiac Rhythm Problems (Arrhythmia Risk).

Overall, the SRP thought the WebEx/teleconference was very helpful and provided a comprehensive overview of the cardiovascular risks. The Risks are being considered in a comprehensive and interdisciplinary manner. The links between the cardiovascular risks and visual impairment are particularly pertinent and seem to be well considered.

The SRP thinks the OI Risk is wrapping up nicely. The additional data being collected on compression garments is likely to be confirmatory, but is nevertheless understandable. The SRP thinks the links between cardiovascular impairment and functional performance are key and the additional information from the Functional Field Test study will be crucial to fully appreciate the implications of this risk.

II. Critique of Gaps and Tasks for the Risk of Orthostatic Intolerance during Re-Exposure to Gravity

1. Have the appropriate targets for closure for the Gaps been identified?
 - a. Are the interim stages appropriate to close the Gaps?
2. Have the proper Tasks been identified to fill the Gaps?
 - a. Are the Tasks relevant?
 - b. Are any Tasks missing?
3. If a Gap has been closed, does the Rationale for Gap Closure provide the appropriate evidence to support the closure?

Gaps and Tasks:

CV3: Is orthostatic intolerance a potential hazard?

- The SRP thinks this Gap is relevant and appropriate.
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- The targets for closure seem to be appropriate.

Tasks:

- Artificial Gravity Exposure Effects on Cardiovascularly Deconditioned Women's and Men's Orthostatic Intolerance Limit – PI: Joyce Evans, Ph.D. – University of Kentucky
- Examining Individual Differences in Temporal Profiles of Cardiovascular Responses to Head Down Tilt During Fluid Loading – PI: Patricia Cowings, Ph.D. – NASA Ames Research Center
- Recovery of Functional Performance Following Long Duration Space Flight – PI: Millard Reschke, Ph.D. – NASA Johnson Space Center
 - The SRP thinks that since blood pressure data is available, it should be scrutinised, particularly in reference to the evaluation of efficacy/equivalency of the compression garments.
- Evaluation of Commercial Compression Garments as a Countermeasure to Post-Spaceflight Orthostatic Intolerance (OIG DSO641) – Task completed
- Efficacy of JOBST Compression Garments to Prevent Orthostatic Intolerance for up to Three Days following 14 Days of Bed Rest – Task completed
- Gender Differences in Bedrest: Autonomic and Neuroendocrine Changes and Vascular Responses in Lower and Upper Extremities – Task completed
- Evaluation of Compression Garments as Countermeasures to Orthostatic Intolerance – Task completed
- Hypovolemia as a Model of Space Flight – Task completed
- Test of Midodrine as a Countermeasure against Postflight Orthostatic Hypotension: SMO-006 – PI: Steven Platts, Ph.D. – NASA Johnson Space Center
- Vestibular-Cerebrovascular Interaction and their Contribution to Post-Spaceflight – Task completed

CV4: Is 1/6-g exposure protective of 1-g orthostatic tolerance?

- The SRP thinks this Gap is relevant and appropriate.
- The SRP thinks it should be clear that this Risk is closed because it is not relevant to current missions, rather than because the question has been answered.

Tasks:

- Lunar Analog Bed Rest Development – Task closed
- Lunar analog pilot study – Task closed

III. The Risk is nearing completion, but the last task will not be completed until 2018. Are there any additional tasks that should be done prior to the Risk closing? Is the remaining task necessary to complete for Risk closure?

The SRP also feels that the remaining task is necessary for Risk closure on CV3 (Is orthostatic tolerance a potential hazard?) and CV4 (Is 1/6-g exposure protective of 1-g orthostatic tolerance?).

The SRP recommends that the HHC Cardiovascular Team obtain more information about the Cardiovascular Reserve Index (Victor A. Convertino, Ph.D. - US Army Institute of Surgical Research). Dr. Convertino has developed a simple, noninvasive finger monitor that uses a machine-learning algorithm to predict OI and this could be applied for HHC purposes.

IV. Discussion on the strengths and weaknesses of the IRP and identify remedies for the weaknesses, including answering these questions:

Is the Risk addressed in a comprehensive manner?

- The SRP thinks the Risk is addressed in a comprehensive manner.

Are there obvious areas of potential integration across disciplines that are not addressed?

- The SRP thinks that the discussion of integration between all of the HHC disciplines (exercise, nutrition, immunology) and the Space Radiation Program Element could be expounded and detailed more in the Research Plan.

V. Evaluation of the progress in the IRP Rev. D since the 2012 SRP meeting.

- The progress since the 2012 meeting is appropriate.

VI. Additional Comments regarding the Risk of Cardiac Rhythm Problems Status Review

The SRP was glad to learn there is ongoing discussion about modifying the Arrhythmia Risk. There is some evidence from the Russian Mir data that there is no basis for this risk. Data from 59 cosmonauts (as reported by Golubchikova et al. (Dynamics of some electrocardiographic parameters in cosmonauts during long-term Mir missions. *Aviakosm Ekolog Med* 37:41–5, 2003)) included electrocardiogram (ECG) tracing on cosmonauts that spent six months or more aboard Mir, and they report "no pathology in the myocardial bioelectrical activity" (Covertino and Cooke, Evaluation of cardiovascular risks of spaceflight does not support the NASA bioastronautics critical path roadmap. *Aviat Space Environ Med.* 2005 Sep;76(9):869-76).

As is, the SRP is not convinced this as an appropriate Risk however, the SRP suggests expanding the Risk to something like "Cardiovascular disease during spaceflight" although using the word "during" may be a problem. Many of these astronauts are middle-aged men and women who may already have otherwise undetected arrhythmias and other cardiovascular risk factors. To say that spaceflight is the cause of certain events, or assumed progression, is going to be very difficult to objectively determine and the SRP does not think the upcoming twin study (albeit n=2) presents an interesting opportunity for this. Another option discussed by the SRP is changing the Risk title to "Influence of spaceflight on cardiovascular disease". Stating the Risk this way would allow for a Gap looking at whether or not long-duration spaceflight increases cardiovascular disease risk upon return from space travel? Additionally, such an identified Gap might allow for some 'data mining' into existing and retired astronauts who are still living, with age/body mass index/gender/etc. and non-astronaut control comparisons (and/or comparisons

within astronauts where flight duration is a primary covariate).

It is clear to the SRP that a comprehensive study is underway and nearing completion. These data will be crucial to appropriately appreciate the true risk. The increased QTc during spaceflight is a potential concern in terms of susceptibility to arrhythmia. It will be important to monitor the time course of this response. The impact on the Tpeak-Tend interval might also be considered, as prolongation of this interval reflects increased transmural dispersion of ventricular repolarisation and has been reported to provide a more robust indicator of arrhythmia risk than QT prolongation (Anzelevitch). Are there potassium derangements during spaceflight that could be considered/remedied? Long term follow-up post-flight will be important to evaluate the implications of cardiac remodelling, particularly during longer duration missions.

VII. Additional Comments

The SRP thinks the OI Risk is well considered, but it seems the data presented are likely to underestimate the true risk because those who are most debilitated by orthostatic hypotension/orthostatic intolerance on landing day are presumably less likely to be fit for testing. Perhaps these data could be incorporated or reported in some way to identify those whose experimental data was not collected because of the very problem under investigation (arguably the population of most interest).

As was discussed during the WebEx/teleconference review, the OI Risk is close to being considered acceptable, providing all countermeasures are employed (exercise in orbit; cooling garments; fluid loading; compression garments; and a medical support team upon landing). The SRP is unsure how this will be mitigated in the event that not all countermeasures are available.

The data on orthostatic intolerance have focussed heavily on heart rate responses. The SRP argues that equally important would be the blood pressure responses and they have been relatively neglected. In those individuals with severe post-flight orthostatic intolerance that progresses to presyncope or syncope, presumably the blood pressure response is key.

The SRP thinks there was little discussion about either of the cardiovascular risks in relation to gender differences, but the SRP is glad to see that a project is underway to address this issue.

Lastly, some of the SRP members do not see the value in deep statistical dives on small N experiments (Twins study). The SRP thinks that high quality data is the key.

VIII. 2013 Cardiovascular Risk SRP Research Plan Review (WebEx/telecon): Statement of Task for the Risk of Orthostatic Intolerance During Re-Exposure to Gravity

The 2013 Cardiovascular Risk Standing Review Panel (SRP) is chartered by the Human Research Program (HRP) Chief Scientist. The purpose of the SRP is to review the Human Health Countermeasures (HHC) Element's section of the current version of the HRP's Integrated Research Plan which is located on the Human Research Roadmap (HRR) website (<http://humanresearchroadmap.nasa.gov/>). Your report will be provided to the HRP Chief Scientist and will also be made available on the HRR website.

The 2013 Cardiovascular Risk SRP is charged (to the fullest extent practicable) to:

1. Based on the information provided in the current version of the HRP's IRP, evaluate the ability of the IRP to satisfactorily address the Risk by answering the following questions:
 - A. Have the proper Gaps been identified to address the Risk?
 - i) Are all the Gaps relevant?
 - ii) Are any Gaps missing?
 - B. Have the appropriate targets for closure for the Gaps been identified?
 - i) Are the interim stages appropriate to close the Gaps?
 - C. Have the proper Tasks been identified to fill the Gaps?
 - i) Are the Tasks relevant?
 - ii) Are any Tasks missing?
 - D. If a Gap has been closed, does the Rationale for Gap Closure provide the appropriate evidence to support the closure?
 - E. The Risk is nearing completion, but the last task will not be completed until 2018. Are there any additional tasks that should be done prior to the Risk closing? Is the remaining task necessary to complete for Risk closure?
2. Identify the strengths and weaknesses of the IRP, *and* identify remedies for the weaknesses, including answering these questions:
 - A. Is the Risk addressed in a comprehensive manner?
 - B. Are there obvious areas of potential integration across HRP disciplines that are not addressed?
3. Please evaluate the progress in the IRP since your 2012 SRP meeting.
4. Please comment on any important issues that are not covered in #1, #2, or #3 above. If addendum questions are provided below, please address each of the questions as fully as possible.

Additional Information Regarding This Review:

1. Expect to receive review materials at least four weeks prior to the WebEx conference call.
2. Participate in a WebEx conference call on October 11, 2013 from 1:00 pm – 4:00 pm ET.
 - A. Discuss the 2013 Cardiovascular Risk SRP Statement of Task and address questions about the SRP process.
 - B. Receive presentations from the HHC Element and participate in a question and answer session.
3. Prepare a draft final report (within one month of the WebEx/teleconference) that contains a detailed evaluation of the current IRP specifically addressing items #1, #2, #3, and #4 of the SRP charge. The draft final report will be sent to the HRP Chief Scientist and he will forward it to the appropriate Element for their review. The HHC Element and the HRP Chief Scientist will have 2 business days to review the draft final report and identify any misunderstandings or errors of fact and then provide official feedback to the SRP. If any misunderstandings or errors of fact are identified, the SRP will have 10 business days to address them and finalize the 2013 SRP Final Report. The 2013 SRP Final Report will be submitted to the HRP Chief Scientist and copies will be provided to the HHC Element that sponsors the cardiovascular discipline and also made available to the other HRP Elements. The 2013 SRP Final Report will be made available on the HRR website (<http://humanresearchroadmap.nasa.gov/>).

IX. 2013 Cardiovascular Risk SRP Status Review Review (WebEx/telecon): Statement of Task for the Risk of Cardiac Rhythm Problems

The 2013 Cardiovascular Risk Standing Review Panel (SRP) will participate in a Status Review that will occur via a WebEx/teleconference with the Human Research Program (HRP) Chief Scientist, Deputy Chief Scientist and members of the Human Health Countermeasures (HHC) Element. The purpose of this review is for the SRP to:

1. Receive an update by the HRP Chief Scientist or Deputy Chief Scientist on the status of NASA's current and future exploration plans and the impact these will have on the HRP.
2. Receive an update on any changes within the HRP since the 2012 SRP meeting.
3. Receive an update by the Element or Project Scientist(s) on progress since the 2012 SRP meeting.
4. Participate in a discussion with the HRP Chief Scientist, Deputy Chief Scientist, and the Element regarding possible topics to be addressed at the next SRP meeting

The 2013 Cardiovascular Risk SRP will produce a report/comments from this status review within 30 days of the 2013 update. These comments will be submitted to the HRP Chief Scientist and copies will be provided to the HHC Element that sponsors the cardiovascular discipline and also made available to the other HRP Elements. The 2013 SRP Final Report will be made available on the Human Research Roadmap public website (<http://humanresearchroadmap.nasa.gov/>).

X. Cardiovascular Risk SRP Research Plan Review WebEx/Teleconference Participants

SRP Members:

Michael Joyner, M.D. (chair) – Mayo Clinic
Jason Carter, Ph.D. – Michigan Technological University
Victoria Claydon, Ph.D. – Simon Fraser University
Ralph Lazzara, M.D. – University of Oklahoma Health Sciences Center
Gail Thomas, Ph.D. – The Heart Institute
Michael Ziegler, M.D. – University of California, San Diego

NASA Ames Research Center (ARC):

NASA Glenn Research Center (GRC):

NASA Headquarters:

NASA Johnson Space Center (JSC):

NASA Research and Education Support Services (NRESS):

Tiffin Ross-Shepard

National Space Biomedical Research Institute (NSBRI):

XI. 2013 Cardiovascular Risk Standing Review Panel Roster

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